Summary of Statistical Review and Evaluation

NDA#:	21-240
Applicant:	Maxim Pharmaceuticals Inc.
Name of Drug:	Histamine dihydrochloride
Indication:	Advanced malignant melanoma
Documents reviewed:	Volumes 2.22, 2.27, 2.28, and 2.57
Medical Officer:	Judy Chiao, M.D.
Statistical Reviewer:	Rajeshwari Sridhara, Ph.D.

ICH E-3 Guidelines: Section 11.4.2.8, Examination of Subgroups

If the size of the study permits, important demographic or baseline value-defined subgroups should be examined for unusually large or small responses and the results presented, e.g. comparison of effects by age, sex, or race, by severity or prognostic groups, by history of prior treatment with a drug of the same class etc. If these analyses were not carried out because the study was too small it should be noted. ***These analyses are not intended to "salvage" an otherwise non-supportive study but may suggest hypotheses worth examining in other studies or be helpful in refining labelling information, patient selection, dose selection etc.***

21 CFR 314.126 (a):

Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is "substantial evidence" to support the claims of effectiveness for new drugs.

Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products: Section IIA:

Substantial evidence was defined in section 505(d) of the Act as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof".

With regard to quantity, it has been FDA's position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness.

Major Statistical Problems with the Study

1. Only one randomized open-label study conducted in patients with metastatic malignant melanoma, which failed to demonstrate efficacy as per the design of the study, in the intent-to-treat population (log-rank test, P-value = 0.1255).
2. When the overall result fails to show efficacy, usually subgroup findings are not acceptable and subgroup analyses at best can be exploratory or hypothesis generating analyses (ICH E-3 guidelines, section 11.4.2.8: *These analyses are not intended to "salvage" an otherwise non-supportive study but may suggest hypotheses worth examining in other studies or be helpful in refining labelling information, patient selection, dose selection etc.*). When one starts to do multiple subgroup testing, one can easily make a false positive claim based on such subgroup analysis. We do not know how to interpret the P-values based on such post-hoc analysis. Furthermore, without replication of the results in a second well-controlled study, the subgroup analysis can not be ruled out for a false positive result.
3. The sponsor wishes to claim approval based on a subgroup of non-randomized patients with liver metastasis. This subgroup hypothesis corresponding to liver metastasis was not stated as a hypothesis of interest to be tested in the original protocol. Any subgroup hypothesis needs to be stated in the protocol and accordingly proper allocation of α has to be specified. Otherwise, such post-hoc subgroup claim will inflate Type I error and it is difficult to interpret such P-values.
4. Some of the important issues not addressed by the sponsor are: lack of stratification prior to randomization and imbalance between the treatment arms with respect to baseline prognostic factors in this subgroup.

1. Background

Effective therapy for melanoma is currently dependent upon early diagnosis. However, a delay in diagnosis can result in the development of metastases. Melanoma can metastasize to most organ systems in the body, including distant lymph nodes, lungs, liver, brain, and bone. The clinical outcome for patients with metastases to distant sites is significantly worse than that seen with regional lymph node metastases. A number of chemotherapeutic agents have been evaluated for the treatment of metastatic melanoma. In general, these agents have been found to have limited effectiveness as single agents or in combination. High-dose Interleukin -2 (IL-2) IV bolus is currently approved regimen for metastatic melanoma.

The rationale for the use of histamine as an adjunct to cytokine therapy with IL-2 in the treatment of certain cancers is based on research program conducted by Kristoffer Hellstrand and colleagues at the Sahlgren's University Hospital in Sweden. There is significant evidence to suggest that lymphocytes capable of recognizing tumor-associated antigens are functionally impaired, or anergized, in melanoma patients.

The sponsor seeks support of subcutaneous administration of histamine dihydrochloride with IL-2 as therapy for the subgroup of metastatic malignant melanoma patients with liver metastasis. In this NDA submission, study MP-US-M01 is the only pivotal study for the efficacy and safety of histamine dihydrochloride and this study will be the focus of this review.

2. Description of Trials

2.1 General Description of All Studies

a) Study MM1: A phase II non-randomized, open-label study conducted in a single center in Sweden, to evaluate the safety and efficacy of IL-2 and INF-α with and without the addition of histamine dihydrochloride in 17 metastatic melanoma patients. This study has been completed.
b) Study MM2: A phase II non-randomized, open label study conducted in a single center in Sweden, to evaluate the safety and efficacy of histamine dihydrochloride, INF-α, and IL-2 in 32 metastatic melanoma patients. This study has been completed.
c) Study MP-MA-103: A phase II open-label single-arm study being conducted at multi centers, to evaluate the safety and efficacy of IL-2 and histamine dihydrochloride. A total of 30-40 advanced metastatic melanoma patients, are planned to be entered into this study. This study is ongoing.
d) Study MP-US-M01: A phase III randomized open-label study to evaluate safety and efficacy of combined IL-2 and histamine dihydrochloride versus IL-2 alone in 300 advanced metastatic melanoma patients.

Reviewer's Comments:

1. Studies MM1 and MM2 were conducted only in one center outside of U.S.. The IL-2 doses used in these two studies were different from the dose used in the randomized M01 study. In addition IFN-α was also administered in these two studies.
2. Study 103 is a non-randomized, single arm open-label study, which is still on-going.
3. Because of the above two reasons, this review will focus only on the randomized study M01 and particularly on the efficacy aspect of this study.

2.2 Detailed Description of Study M01

This study was designed to evaluate the efficacy and safety of combined immunotherapy with histamine dihydrochloride + IL-2 versus IL-2 alone in patients with metastatic melanoma. This was a multi-center, randomized, controlled, open-label, parallel group study. All patients received the same dose and regimen of IL-2 in 6-week cycles (Weeks 1 and 3, Days 1 and 2: 9.0 mIU/m^2 BID by self-administered subcutaneous (SC) injection; Weeks 2 and 4, Days 1-5: 2.0 mIU/m^2 BID by self-administered SC injection; Weeks 5 and 6: no treatment). For those patients randomized to receive histamine, the dose was 1.0 mg BID by slow self-administered SC injection following each IL-2 dose. Patients were monitored weekly for safety, including performance status (PS) and laboratory assessments, and could continue treatment up to 12

months (8 cycles) or until a confirmed complete remission (CR), progressive disease (PD), or life-threatening toxicity occurred (Sponsor section 7.1, page 25, volume 2.22).

2.2.1 Objectives

The objectives of this study were: 1) To evaluate the clinical efficacy of SC histamine dihydrochloride given in conjunction with SC recombinant human IL-2 as compared to SC IL-2 alone in patients with advanced metastatic melanoma. 2) To characterize the safety and toxicities including dose-limiting toxicities, should any occur, of SC histamine dihydrochloride given in conjunction with SC IL-2 compared to SC IL-2 alone. 3) To evaluate the quality of well-being before and periodically during the study. (Sponsor section 2.0, page 135, volume 2.22)

Reviewer's Comments:

In the original protocol there were no plans to claim efficacy based on subgroups. Proper allocation of α values for multiple subgroup hypotheses testing was not considered in the protocol.

2.2.2 Sample Size Considerations

In the original protocol, a sample size of 96 patients in each group was determined to be sufficient to detect of 50% increase in median survival time (7.3 months to 11 months) between two treatment groups with a type I error of 0.05. Making an adjustment for an expected dropout rate of 20%, enrollment of 240 patients (120 per group) was planned to maintain the desired power. However, with an accrual time of 18 months, and 12 months of follow-up, it was re-estimated that a sample size of 252 patients (126 patients per group) would be required to provide statistical power of 80% to detect a 50% increase in median survival time (7.3 months to 11 months) between the two treatment groups with a type I error rate of 0.05. Adjusting for an expected dropout rate of approximately 15%, 300 patients (150 patients per group) was required to maintain the desired power. (Sponsor section 7.7.6, page 51, volume 2.22)

Reviewer's Comments:

1. The sample size computation was not based on number of events. The protocol did not specify the time of final analysis. The current cut off date of March 8, 2000 seems to be some what arbitrary.
2. The study enrolled a total of 305 patients with 153 patients who received IL-2 alone and 152 patients who received IL-2 + histamine dihydrochloride.

2.2.3 Randomization

Patients entering the study were randomly assigned to one of the two treatment arms. The randomization table was prepared by a statistician in blocks of four at each center so that within each block of four, two patients would be randomized into each treatment arm. The randomization was controlled from a single location, administered by [ ].

After determining eligibility for enrollment for any particular patient, principal investigators telephoned [ ] to determine assignment to treatment arm. Therapy was to start within two weeks following randomization. (Sponsor section 7.4.3, page 34, volume 2.22)

Reviewer's Comments:

Although two stratification factors, presence or absence of liver metastasis, and prior DTIC or no DTIC therapy, were specified in the protocol, the randomization was not stratified by these two factors. This can potentially result in imbalances in known and unknown prognostic factors within these subgroups.

2.2.4 Efficacy Endpoints

The primary efficacy endpoint was survival. Survival was defined as time between date of randomization and date of death. In the case of censored patients, the data cut-off date was March 8, 2000.

Secondary efficacy endpoints were time to tumor progression of disease, tumor-free survival, tumor response rates and quality of well-being of the patients.

2.2.5 Interim Analysis

Per protocol, the data safety monitoring board (DSMB) was planned to conduct an interim analysis for efficacy when one-half of patients (100-evaluable patients) completed the study. The interim analysis was to be conducted using 0.015 alpha level, and final analysis to be conducted at 0.042 alpha level. This adjustment for alpha was planned according to O'Brien-Fleming testing procedures.

However, a safety interim analysis was performed and included data for the first 20 randomized patients who completed one cycle of therapy. Four additional patients were included who had data in the clinical database at the designated cutoff date (January 9, 1998). The primary variable was adverse events. Demographic, baseline characteristics, performance status, concomitant medications, and reasons for discontinuations were also presented. This safety interim analysis was submitted to FDA on April 14, 1998.

It is also reported that one investigator analyzed survival data from 40 patients recruited at his site and submitted an abstract to the 2000 meeting of American Society of Oncology. This was done 7 months after recruitment into the study was completed. (Sponsor section 7.7.7.3, pages 52-53, volume 2.22)

Reviewer's Comments:

1. The results of the planned efficacy interim analysis was not reported in the NDA submission. According to protocol specified allocation of α, the significance level for the final survival analysis should be 0.042 and not 0.05.

2. Safety interim analysis reported above is unlikely to have influenced the final results of the study.

2.2.6 Efficacy Analysis Methods

Per protocol, efficacy analysis was to be conducted on both the Intent-to-treat (ITT) and efficacy-evaluable populations. The primary efficacy parameter was survival time of patients. Life table procedures were to be utilized to analyze survival data. The comparison of survival distribution between treatment groups was to be evaluated using a log-rank test. The survival curves were also to be adjusted for prognostic variables such as cutaneous, GI and nodal lesions and pulmonary lesions based on the location of the patient's metastatic disease at first evaluation using Cox's proportional hazard model. Results were also to be displayed stratified by patients presenting with liver metastasis versus patients with no liver metastasis, and patients previously treated with DTIC versus DTIC naïve patients. (Sponsor, appendix G, section 4, page 190, volume 2.22).

The secondary endpoints, time to progression of the disease and tumor-free survival, were also to be analyzed using life-table procedures.. Overall tumor response rate was to be compared between the two treatment groups using a chi-square test. Duration of response between the two treatment groups was to be compared using t-test. Quality of patient's well-being was to be analyzed using appropriate statistical methods. (Sponsor, appendix G, section 4, page 191, volume 2.22).

Reviewer's Comments:

1. In the original protocol there were no plans to claim efficacy based on subgroups. Furthermore, tests of hypotheses of difference between treatment arms with respect to survival in these subgroups were not stated. Proper allocation of α values for multiple subgroup hypotheses testing was not considered in the protocol.
2. FDA had conveyed to the sponsor that efficacy with respect to overall survival in the ITT population had to be demonstrated using unadjusted analysis and that statistically significant survival advantage in a single subgroup will not lead to approval (Meeting minutes, October 20, 1999).
3. FDA had advised the sponsor to stratify prior to randomization to avoid imbalances, for factors identified in the subgroup analyses, namely presence or absence of liver metastasis, and previously treated or not treated with DTIC. The agency had also conveyed that it requires two adequate and well controlled trials for approval of a drug (Meeting minutes April 9, 1997).
4. FDA had also conveyed to the sponsor that the duration of response between the two treatment groups is not meaningful since the outcome is treatment dependent and the comparison will be based on responders only (Response dated December 17, 1999).

3 Efficacy Results of Study M01

3.1 Demographic and Other Baseline Characteristics

The demographic and baseline characteristics are as presented in Table 1a for the ITT population and for the subgroup population with baseline liver metastasis (ITT-LM) (Sponsor's Table 6, page 61, volume 2.22).

Reviewer's Comments:

1. With respect to demographic and baseline characteristics, there was statistically significant imbalance between the two treatment arms in the **ITT** population in the number of patients who presented with or without liver metastasis, ***favoring the histamine + IL-2 group*** (Reviewer's analysis, Table 1b, Fisher's exact test, P-value=0.037). There were no significant imbalances in the number of patients between the two treatment arms in the ITT population subgroups of age (< 65 years versus ≥ 65 years), baseline LDH (< ULN versus ≥ ULN), baseline PS (0 versus 1), Sex (Male versus female), prior chemotherapy (yes versus no), baseline albumin (4 versus ≥ 4), and skin, lymph node, bone, lung, or CNS metastasis (present versus not present).

2. With respect to demographic and baseline characteristics, there was statistically significant imbalance between the two treatment arms in the **ITT-LM** population in the number of patients who presented with one metastatic site versus those presented with more than one metastatic site, ***favoring the histamine + IL-2 group*** (Reviewer's analysis, Table 1b, Fisher's exact test, P-value=0.047). There were imbalances, although not statistically significant, in the number of patients between the two treatment arms, with respect to age group, baseline LDH measurements, baseline performance status, sex, prior chemotherapy, number of metastatic sites, baseline albumin, lymph node and CNS metastases, disease-free survival since the initial diagnosis of primary tumor to diagnosis of initial metastasis, baseline albumin and time since initial metastasis to randomization, all favoring the histamine + IL-2 arm, except for LDH. Besides these there could be other factors not considered here, which may result in the observed difference in survival.

3. There are errors in Sponsor's Table 4 and Table 5, pages 22 and 24, Volume 2.57, respectively, listing demographics and baseline characteristics for study M01 in the ITT population and ITT-LM population, in the number of patients reported in the LDH < ULN and LDH ≥ ULN groups. The numbers reported in Sponsor's Table 6, page 61, volume 2.22, are verified to be correct.

Table 1a: Demographic and Baseline Characteristics: ITT and ITT-LM populations (Sponsor's Table)

Characteristic	ITT		ITT-LM	
	IL-2	Histamine + IL-2	IL-2	Histamine + IL-2
	N=153	N=152	N=74	N=55
Age (yrs)				
Mean (SD)	56.3 (13.12)	53.6 (13.79)	57.6 (13.3)	53.7 (14.37)
Min – Max	21 – 89	22-84	25 – 88	31-79
Age ≥ 65 years (%*)	50 (33)	35 (23)	28 (38)	13 (24)
N	153	152	74	55
Race [n(%*)]				
Caucasian	147 (96)	148 (97)	71 (96)	54 (98)
Black	0	1 (< 1)	0	1 (2)
Asian	0	0	0	0
Other	6 (4)	3 (2)	3 (4)	0
N	153	152	74	55
Sex [n(%*)]				
Male	99 (65)	90 (59)	46 (62)	27 (49)
Female	54 (35)	62 (41)	28 (38)	28 (51)
N	153	152	74	55
WHO Performance Status[n(%)]				
PS 0 (KPS 100-90)	103 (67)	103 (68)	44 (59)	35 (64)
PS 1 (KPS 80-70)	50 (33)	48 (32)	30 (41)	19 (35)
N	153	151	74	54
Disease Sites [n(%*)]				
Skin	40 (26)	47 (31)	18 (24)	12 (22)
Lymph node	83 (54)	77 (51)	38 (51)	24 (44)
Bone	11 (7)	19 (13)	8 (11)	5 (9)
Lung	90 (59)	99 (65)	47 (64)	32 (58)
Liver**	74 (48)	55 (36)	74 (100)	55 (100)
CNS	10 (7)	12 (8)	6 (8)	1 (2)
Other	76 (50)	62 (41)	37 (50)	22 (40)
Number of metastatic sites**[n(%*)]				
1	31 (20)	37 (24)	7 (9)	13 (24)
2	47 (31)	48 (32)	17 (23)	12 (22)
> 2	75 (49)	67 (44)	50 (68)	30 (55)
Mean (SD)	2.7 (1.43)	2.7 (1.71)	3.3 (1.50)	3.1 (2.02)
Min – Max	1 – 7	1 – 10	1 – 7	1 – 10
N	153	152	74	55
Time since first diagnosis for the primary disease (years) [n(%*)]				
0-2	64 (42)	49 (32)	27 (36)	11 (20)
3-4	37 (24)	42 (28)	21 (28)	18 (33)
> 4	47 (31)	54 (36)	25 (34)	22 (40)
Unknown	5 (3)	7 (5)	1 (1)	4 (7)
Mean (SD)	4.4 (5.98)	4.5 (4.54)	5.0 (7.08)	5.2 (4.46)
Median	2.37	3.11	2.72	3.52
Min – Max	0.0 – 38.1	0.1 – 30.3	0.1 – 38.1	0.1 – 20.0
N	148	145	73	51
Prior Chemotherapy [n(%*)]				
Yes	38 (25)	40 (26)	21 (28)	10 (18)
N	153	152	74	55
Number of prior anti-cancer therapies from date of diagnosis				
Mean (SD)	4.0 (2.38)	4.5 (2.91)	3.9 (2.36)	3.9 (2.87)
Median	4.0	4.0	3.0	3.0
Min – Max	0 – 13	0 – 15	0 – 13	0 – 15
N	153	152	74	55
LDH (U/L) [n(%*)]				
≥ ULN	57 (40)	52 (36)	38 (56)	32 (63)
N	143	144	68	51

* Column percentages; ** See reviewer's comments 2 and 3 above.

Table 1b: Distribution of Patients With Respect to Baseline Characteristics in the ITT and ITT-LM Populations by Treatment Groups

Characteristic	ITT			ITT-LM		
	IL-2 [N (%*)]	Histamine + IL-2 [N(%*)]	P-value**	IL-2 [N(%*)]	Histamine + IL-2 [N(%*)]	P-value**
Age Group						
< 65 yrs	103 (67.3)	117 (77.0)	0.074	46 (62.2)	42 (76.4)	0.126
>=65 yrs	50 (32.7)	35 (23.0)		28 (37.8)	13 (23.6)	
LDH Group						
<UNL	86 (60.1)	92 (63.9)	0.544	30 (44.1)	19 (37.3)	0.573
>=UNL	57 (39.9)	52 (36.1)		38 (55.9)	32 (62.7)	
Baseline PS						
0	103 (67.3)	103 (68.2)	0.903	44 (59.5)	35 (64.8)	0.584
1	50 (32.7)	48 (31.8)		30 (40.5)	19 (35.2)	
Sex						
Male	99 (64.7)	90 (59.2)	0.347	46 (62.2)	27 (49.1)	0.154
Female	54 (35.3)	62 (40.8)		28 (37.8)	28 (50.9)	
Prior Chemo						
No	115 (75.2)	112 (73.7)	0.794	53 (71.6)	45 (81.8)	0.214
Yes	38 (24.8)	40 (26.3)		21 (28.4)	10 (18.2)	
# of Met. Sites						
1	31 (20.3)	37 (24.3)	0.412	7 (9.5)	13 (23.6)	**0.047**
> 1	122 (79.7)	115 (75.7)		67 (90.5)	42 (76.4)	
Base Albumin						
< 4	70 (45.8)	60 (39.5)	0.298	41 (55.4)	23 (41.8)	0.155
> = 4	83 (54.2)	92 (60.5)		33 (44.6)	32 (58.2)	
Skin						
No	113 (73.9)	105 (69.1)	0.377	56 (75.7)	43 (78.2)	0.834
Yes	40 (26.1)	47 (30.9)		18 (24.3)	12 (21.8)	
Lymph node						
No	70 (45.8)	75 (49.3)	0.567	36 (48.6)	31 (56.4)	0.476
Yes	83 (54.2)	77 (50.7)		38 (51.4)	24 (43.6)	
Bone						
No	142 (92.8)	133 (87.5)	0.129	66 (89.2)	50 (90.9)	1.000
Yes	11 (7.2)	19 (12.5)		8 (10.8)	5 (9.1)	
Lung						
No	63 (41.2)	53 (34.9)	0.289	27 (36.5)	23 (41.8)	0.586
Yes	90 (58.8)	99 (65.1)		47 (63.5)	32 (58.2)	
Liver						
No	79 (51.6)	97 (63.8)	**0.037**			
Yes	74 (48.4)	55 (36.2)		74 (100)	55 (100)	
CNS						
No	143 (93.5)	140 (92.1)	0.665	68 (91.9)	54 (98.2)	0.237
Yes	10 (6.5)	12 (7.9)		6 (8.1)	1 (1.8)	
Disease-free survival* **						
< 1 year	54 (35.3)	48 (31.6)	0.544	22 (29.7)	13 (23.6)	0.549
≥ 1 year	99 (64.7)	104 (68.4)		52 (70.3)	42 (76.4)	
Baseline Albumin						
< 4 g/dL	70 (45.8)	60 (39.5)	0.298	41 (55.4)	23 (41.8)	0.155
≥ 4 g/dL	83 (54.2)	92 (60.5)		33 (44.6)	32 (58.2)	
Time from initial met. to randomization						
< 1 year	121 (79.1)	119 (78.3)	0.890	64 (86.5)	43 (78.2)	0.243
≥ 1 year	32 (20.9)	33 (21.7)		10 (13.5)	12 (21.8)	

* Column percentage; ** Fisher's exact test; *** Disease-free survival from the diagnosis of primary tumor to initial metastasis;

3.2 Primary Efficacy Evaluation - Survival Analyses

The primary efficacy variable was the duration of survival. This was applied to two populations, namely ITT and ITT-LM, by the sponsor. The cut-off date for data was March 8, 2000 and data for all patients on this date were censored. There was no statistically significant difference between the two treatment arms in the ITT population (log-rank test, P-value=0.1255, Figure 1, Table 2a). There appears to be significant difference in survival between the two treatment arms in the non-randomized subgroup ITT-LM population (log-rank test, P-value=0.004, Figure 2, Table 2b). According to the sponsor, no patient was lost to follow-up.

Reviewer's Comments:

1. Histamine + IL-2 treatment failed to demonstrate superior survival over IL-2 alone in the randomized ITT population (Figure 1 and Table 2a below).

2. Histamine + IL-2 treatment appears to have better survival compared to IL-2 treatment in the non-randomized subgroup of patients who presented with liver metastasis at baseline. (Figure 2 and Table 2b below). There was no significant difference in survival between the two treatment arms in the subgroup of patients who presented with no liver metastasis at baseline (Figure 3 and Table 2c below). However, the estimated median survival was in favor of IL-2 alone arm (10.3 months in the IL-2 alone arm versus 8.7 months in the histamine + IL-2 arm).

3. ICH E– 3, Section 11.4.2.8, clearly specifies guidelines for conducting subgroup analyses, namely, '***These analyses are not intended to "salvage" an otherwise non-supportive study but may suggest hypotheses worth examining in other studies or be helpful in refining labelling information, patient selection, dose selection etc.*** ' This reviewer believes that the results of analysis based on a subgroup of patients with liver metastasis when the overall study is not-supportive, is not acceptable. There are several other concerns regarding this subgroup analysis: (a) The study was not stratified prior to randomization with respect to baseline liver involvement; (b) In the ITT-population, there was statistically significant imbalance between the two treatment arms with respect to number of patients who presented with liver metastasis, favoring the histamine + IL-2 arm; and (c) In the ITT-LM population, there was statistically significant imbalance between the two treatment arms with respect to the number patients presenting with one metastatic disease site, favoring the histamine + IL-2 arm.

4. The impact of 20 patients (7 in the IL-2 arm and 13 in the histamine + IL-2 arm) with only one metastatic site has been examined. The difference in survival in the liver metastasis subgroup appears to come from sub-sub group of patients with one metastatic site (P-value = 0.0006, Table 2c). If we exclude these 20 patients, then there was no significant difference in survival between the two treatment arms in the subgroup ITT-LM patients (P-value=0.08, Table 2c below). The question then arises if we should consider the treatment only for the sub-sub group of patients with only liver metastasis and no other site involved.

5. Apparent differences in survival with small p-values between the two treatment arms were also present in subgroups of the ITT-population, other than those with liver metastasis (Table 3). The question arises if we should consider these subgroups seriously.

Figure 1
Kaplan-Meier Plot of Duration of Survival in ITT Population

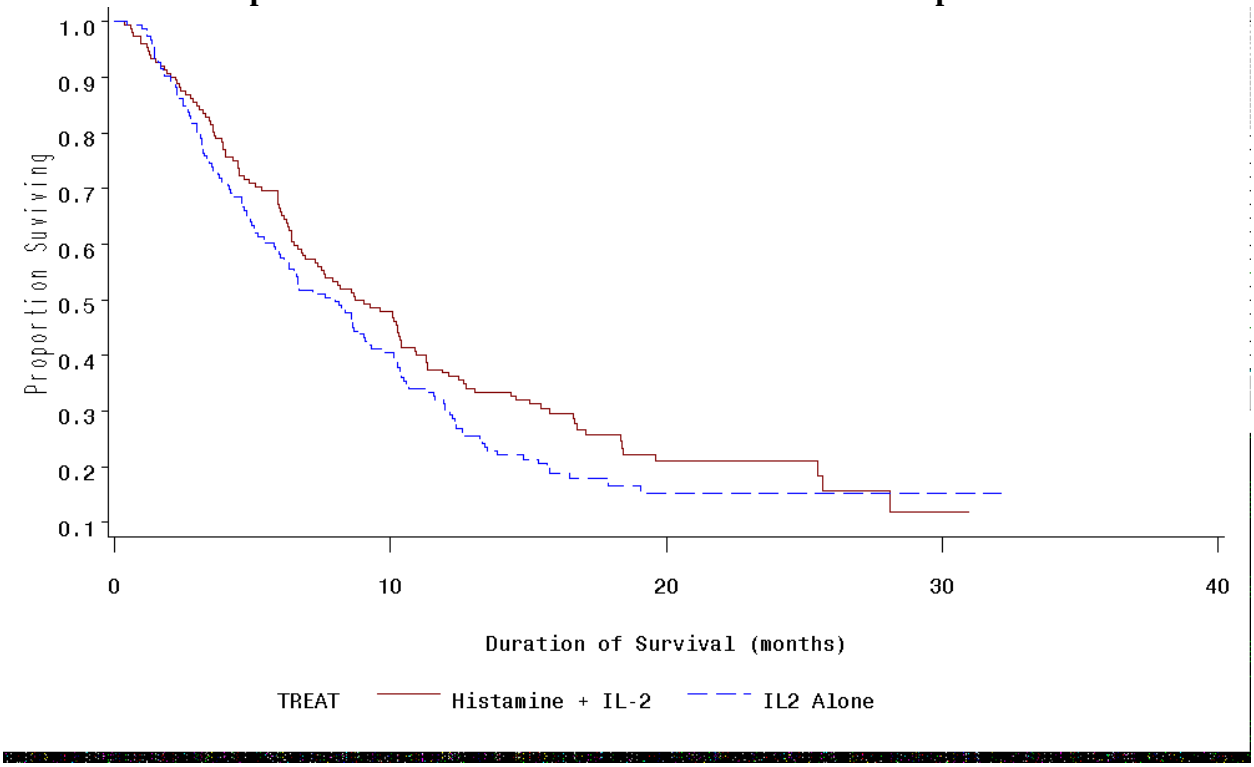

Table 2a: Kaplan-Meier Estimates of Median Duration of Survival (in Months)

ITT Population	IL-2	IL-2 + Histamine	Hazard Ratio* (95% C.I.)	Unadjusted P-value (Log-rank test)
N	153	152		
Number who died	126	117		
Number censored	27	35		
Median (95% C.I.)	8.0 (6.0, 9.2)	8.9 (6.9, 10.4)	0.822 (0.638, 1.051)	0.1255

* Hazard Ratio = Histamine + IL-2/ IL-2

Figure 2
Kaplan-Meier Plot of Duration of Survival in ITT-LM Population

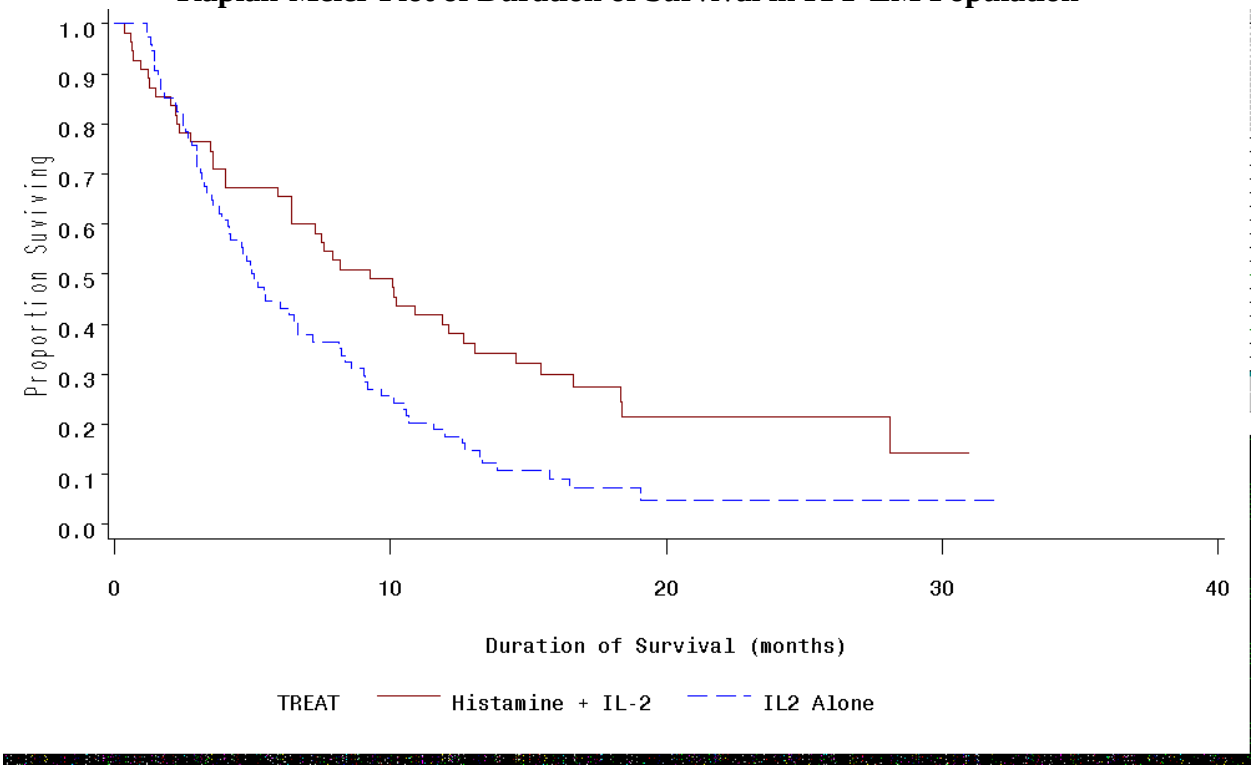

Table 2b: Kaplan-Meier Estimates of Median Duration of Survival (in Months)

Population	IL-2	IL-2 + Histamine	Hazard Ratio* (95% C.I.)	Unadjusted P-value (Log-rank test)
ITT-liver metastasis				
N	74	55		
Number who died	69	42		
Number censored	5	13		
Median (95% C.I.)	5.0 (3.9, 6.7)	9.2 (6.4, 12.7)	0.568 (0.383, 0.835)	0.0040
ITT- No liver metastasis				
N	79	97		
Number who died	57	75		
Number censored	22	22		
Median (95% C.I.)	10.3 (8.6, 12.3)	8.7 (6.6, 10.4)	1.142 (0.811, 1.600)	0.4493

- Hazard Ratio = Histamine + IL-2 / IL-2

Figure 3
Kaplan-Meier Plot of Duration of Survival in ITT with NO Liver Metastasis Population

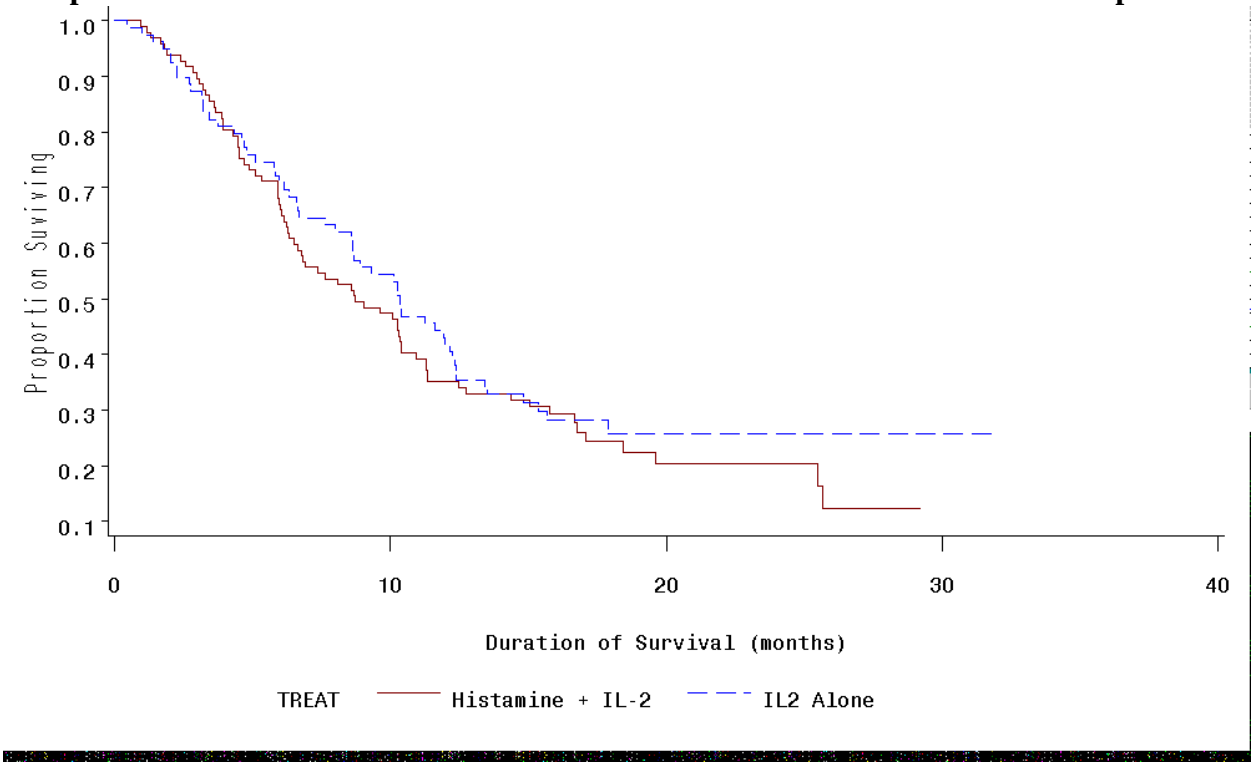

Table 2c: Kaplan-Meier Estimates of Median Duration of Survival (in Months)

Population	IL-2	IL-2 + Histamine	Hazard Ratio* (95% C.I.)	Unadjusted P-value (Log-rank test)
ITT- Liver metastasis with > 1 metastatic site				
N	67	42		
Number who died	62	33		
Number censored	5	9		
Median (95% C.I.)	5.5 (4.2, 8.2)	7.7 (4.0, 11.9)	0.681 (0.445, 1.051)	0.0757
ITT- Liver metastasis with 1 metastatic site				
N	7	13		
Number who died	7	9		
Number censored	0	4		
Median (95% C.I.)	3.8 (3.0, 4.6)	16.6 (6.4, 28.1)	0.091 (0.018, 0.468)	0.0006

* Hazard Ratio = Histamine + IL-2 / IL-2

Table 3: Estimates of Median Survival (in months) in Subgroups of ITT Population with Statistically Significant Differences between the two Treatment Groups

Subgroup	IL-2	IL-2 + Histamine	P-value (Log-rank test)
Age ≥ 65 years	6.6 (n=50)	10.1 (n=35)	0.046
No Bone metastasis	8.3 (n=142)	10.1 (n=133)	0.035
No Lung metastasis	6.7 (n=63)	10.4 (n=53)	0.025

3.3 Covariate Adjusted Survival Analyses

Selected baseline characteristics were investigated by the sponsor in a multivariate test to evaluate the impact of multiple factors on survival outcome. The results of these multivariate analyses are presented in Tables 4 and 5 (Sponsor's Tables 8 and 9, page 67, volume 2.22).

Table 4: Cox's Proportional Hazard Model Adjusting for Covariates in the ITT Population (Sponsor's Model)

Covariates	Hazard Ratio	95% C.I.	P-value**
Treatment (Histamine+Il-2 vs IL-2)	0.776	0.595 – 1.012	0.0612
Sex (male vs female)	1.539	1.154 – 2.053	0.0034
LDH (≥ ULN vs < ULN)*	2.311	1.747 – 3.057	0.0001
Baseline Performance Status (1 vs 0)*	2.140	1.608 – 2.848	0.0001
Geographic Region			
Mid-West vs South	1.182	0.731 – 1.910	0.4957
North vs South	0.899	0.562 – 1.439	0.6586
West vs South	0.793	0.518 – 1.213	0.2854
Disease Sites			
Lymph Node (Yes vs No)*	1.536	1.170- 2.015	0.0020
Bone (Yes vs No)*	2.314	1.482 – 3.613	0.0002

* significant prognostic indicator from sponsor's univariate analysis

** P-values not adjusted for multiplicity

Table 5: Cox's Proportional Hazard Model Adjusting for Covariates in the ITT-LM Population (Sponsor's Model)

Covariates	Hazard Ratio	95% C.I.	P-value**
Treatment (Histamine+Il-2 vs IL-2)	0.499	0.324 – 0.769	0.0017
LDH (≥ ULN vs < ULN)*	2.288	1.482 – 3.531	0.0002
Baseline Performance Status (1 vs 0)*	2.402	1.572 – 3.670	0.0001
Geographic Region			
Mid-West vs South	0.875	0.413 – 1.853	0.7273
North vs South	1.184	0.565 – 2.481	0.6541
West vs South	1.051	0.545 – 2.027	0.8816
Disease Sites			
Bone (Yes vs No)*	4.406	2.226 – 8.722	0.0001
Prior anti Cancer Therapy (yes vs no)	0.296	0.100 – 0.875	0.0277

* significant prognostic indicator from sponsor's univariate analysis

** P-values not adjusted for multiplicity

Reviewer's Comments:

1. Per original protocol, only two prognostic factors, liver metastasis and prior chemotherapy, were specified for the adjusted survival analyses. Table 6 presents the result of this adjusted Cox regression analysis.

Table 6: Cox's proportional hazard model per protocol in the ITT population

Covariates	Hazard Ratio	95% C.I.	P-value
Treatment (IL-2 + Histamine vs IL-2)	0.820	0.638, 1.051	0.1228
Liver metastasis (Yes vs No)	1.500	1.162, 1.916	0.0017
Prior Chemotherapy (Yes vs No)	1.355	1.020, 1.786	0.0364

2. The sponsor's model selection procedure is questionable. The sponsor has chosen to include in multivariate model, variables that were not significant in the univariate analyses, and even though not significant, the treatment was also included in the selected model. The baseline LDH in these patients had a skewed distribution in both the treatment arms. Table 7 gives the mean, standard deviation, median, range and skewness parameter in both the ITT and ITT-LM populations by treatment arm. Thus it is appropriate to analyze the LDH data by transforming the LDH measurements to Log_e (LDH). When the LDH group variable used in the sponsor's models (Tables 4 and 5) was replaced with Log_e (LDH), and the factor region was removed from the model, the reduction in P-value that the sponsor has claimed with the adjusted analyses was not observed (Tables 8 and 9).

Table 7: Distribution of Baseline LDH (U/L)

Parameter	ITT		ITT-LM	
	IL-2 N=143	IL-2 + Histamine N=144	IL-2 N=68	IL-2 + Histamine N=51
Mean	401	406	515	499
Standard Deviation	526	583	685	513
Median	200	191	261	279
Range	97 – 4296	90 – 5430	97-4296	101 - 2141
Skewness	4.43	5.30	3.67	1.97

Table 8: Cox's Proportional Hazard Model in the ITT Population Adjusting for Covariates with Log_eLDH and Removing Region from the Sponsor's Model in Table 6

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (Histamine+Il-2 vs IL-2)	0.820	0.631, 1.062	0.1387
Sex (male vs female)	0.752	0.566, 0.990	0.0436
Log_eLDH	1.737	1.462, 2.054	0.0001
Baseline Performance Status (1 vs 0)	2.140	1.616, 2.829	0.0001
Disease Sites			
Lymph node (Yes vs No)	1.616	1.234, 2.117	0.0005
Bone (Yes vs No)	2.153	1.391, 3.353	0.0006

* P-value not adjusted for multiplicity

Table 9: Cox's Proportional Hazard Model in the ITT-LM Population Adjusting for Covariates with Log_eLDH and Removing Region from the Sponsor's Model in Table 6

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (Histamine+Il-2 vs IL-2)	0.589	0.391, 0.887	0.0123
Log_eLDH	1.563	1.234, 1.994	0.0002
Baseline Performance Status (1 vs 0)	2.408	1.584, 3.669	0.0001
Disease Sites			
Bone (Yes vs No)	3.692	1.896, 7.243	0.0001
Prior anti Cancer Therapy (yes vs no)	0.412	0.142, 1.185	0.1014

* P-value not adjusted for multiplicity

3. As noted in Section 3.1 above, there were imbalances in the distribution of patients between the two treatment arms with respect to baseline performance status, number of disease sites, baseline LDH, lymph node, lung and CNS metastases, disease-free survival since the initial diagnosis of the primary tumor to initial metastasis, baseline albumin and time from initial metastasis to randomization, in the ITT-LM subgroup population. Thus it is appropriate to adjust the treatment effect for these covariates in the Cox proportional hazard model. The results of this analysis are presented in Table 10. Again after adjusting for these factors with distribution imbalance, the P-value for the treatment difference in the liver metastasis subgroup increases to 0.1193 from the unadjusted p-value=0.004. This P-value can not be taken at face value as it is not adjusted for multiple hypotheses testing, and multiple covariate analyses, and hence it is difficult to interpret.

Table 10: Cox's Proportional Hazard Model in the ITT-LM Population Adjusting for Covariates with Imbalance

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (Histamine+Il-2 vs IL-2)	0.700	0.447, 1.096	0.1193
Age Group (≥ 65 yrs vs < 65 yrs)	1.380	0.880, 2.164	0.1611
Sex (male vs female)	1.003	0.663, 1.516	0.9892
Baseline Performance Status (1 vs 0)	1.986	1.246, 3.167	0.0039
Number of metastatic sites	0.998	0.845, 1.178	0.9814
Log_eLDH	1.687	1.298, 2.192	0.0001
Lymph node (yes vs no)	1.672	1.035, 2.072	0.0356
Lung (yes vs no)	1.167	0.701, 1.942	0.5529
CNS (yes vs no)	1.065	0.457, 2.484	0.8845
Prior Chemotherapy	1.249	0.733, 2.129	0.4126
Disease-free Survival since the initial diagnosis of the primary tumor (≥ 1 yr vs < 1 yr)	0.609	0.378, 0.981	0.0415
Baseline Albumin	0.760	0.456, 1.267	0.2929
Time from initial met to randomization (≥ 1 yr vs < 1 yr)	0.816	0.470, 1.414	0.4680

* P-value not adjusted for multiplicity

4. This reviewer also conducted a covariate adjusted analysis by including significant prognostic factors referenced in literature in advanced malignant melanoma patients. The adjusted model for ITT population is presented in Table 11a. According to ICH guidelines E-9 Section 5.7, subgroup or interaction analyses are exploratory and they should explore the

uniformity or consistency of any treatment effects found overall. In this case there is no overall treatment effect. However, an exploratory analysis was conducted including the interaction between treatment and liver involvement (Table 11b). The model presented in Table 11a differs from the Sponsor's model (Table 4) and it is to be noted that treatment was not a significant factor. The presence or absence of liver metastasis, and prior chemotherapy, were also not significant factors in this model. The adjusted model for ITT-LM population is presented in Table 12. This model differs from the Sponsor's model and for the treatment effect, the p-value was larger and hazard ratio was greater than that reported in the sponsor's analysis (Table 5). Prior chemotherapy was not a significant factor in this model. There is no convincing evidence to suggest that the treatment is effective in the ITT-LM population.

Table 11a: Cox's Proportional Hazard Model Adjusting for Covariates in the ITT Population

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (Histamine + IL-2 vs IL-2)	0.819	0.612, 1.096	0.1798
Liver metastasis (yes vs no)	1.030	0.761, 1.394	0.8480
Baseline Albumin	0.789	0.568, 1.096	0.1572
Baseline Performance Status (1 vs 0)	1.911	1.424, 2.565	0.0001
Log_eLDH	1.645	1.374, 1.968	0.0001
Prior chemotherapy (yes vs no)	1.060	0.777, 1.445	0.7128
Number of metastatic sites	1.163	1.070, 1.264	0.0004
Sex (Male vs Female)	0.717	0.542, 0.949	0.0199
Age Group (³ 65 yrs vs < 65 yrs)	1.186	0.879, 1.600	0.2647
Disease-free survival since the initial diagnosis of primary tumor (< 1 yr vs ³ 1 yr)	1.154	0.861, 1.545	0.3373
Skin/lymph node/lung only (yes vs no)	1.135	0.708, 1.819	0.5982

* P-value not adjusted for multiplicity.

Table 11b: Cox's Proportional Hazard Model Adjusting for Covariates in the ITT Population -Interaction Between Treatment and Liver Involvement Included

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (Histamine + IL-2 vs IL-2)	1.084	0.715, 1.644	0.7031
Liver metastasis (yes vs no)	2.263	0.917, 5.586	0.0765
Treatment ´ Liver met. interaction	0.579	0.321, 1.046	0.0700
Baseline Albumin	0.828	0.595, 1.153	0.2634
Baseline Performance Status (1 vs 0)	1.976	1.467, 2.661	0.0001
Log_eLDH	1.636	1.367, 1.958	0.0001
Prior chemotherapy (yes vs no)	1.049	0.770, 1.429	0.7619
Number of metastatic sites	1.153	1.058, 1.255	0.0011
Sex (Male vs Female)	0.725	0.549, 0.959	0.0241
Age Group (³ 65 yrs vs < 65 yrs)	1.185	0.879, 1.599	0.2656
Disease-free survival since the initial diagnosis of primary tumor (< 1 yr vs ³ 1 yr)	1.156	0.863, 1.547	0.3307
Skin/lymph node/lung only (yes vs no)	0.961	0.586, 1.575	0.8752

* P-value not adjusted for multiplicity.

Table 12: Cox's Proportional Hazard Model Adjusting for Covariates in the ITT-LM Population

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (Histamine + IL-2 vs IL-2)	0.680	0.442, 1.048	0.0806
Baseline Albumin	0.718	0.430, 1.199	0.2053
Baseline Performance Status (1 vs 0)	2.074	1.307, 3.291	0.0020
Log_eLDH	1.586	1.241, 2.027	0.0002
Prior chemotherapy (yes vs no)	1.134	0.684, 1.882	0.6253
Number of metastatic sites	1.083	0.962, 1.219	0.1889
Sex (Male vs Female)	0.927	0.618, 1.390	0.7135
Age Group (³ 65 yrs vs < 65 yrs)	1.371	0.881, 2.134	0.1616
Disease-free survival since the initial diagnosis of primary tumor (< 1 yr vs ³ 1 yr)	0.677	0.428, 1.070	0.0950

* P-value not adjusted for multiplicity.

3.4 Evaluation of Secondary Efficacy Parameters

3.4.1 Time to Progression

Time to progression was defined in two different ways: 1) Time to first progression was defined as the time between the randomization date and the first observed response of progressive disease from week 12 or later, or death due to melanoma. 2) Time to last progression was defined as the time between the randomization date and the last response of observed progressive disease from week12 or later, or death due to melanoma. The following results (Tables 13 and 14) have been reported by the sponsor with respect to time to progression analyses. (Sponsor Tables 16 and 18, pages 76 and 79, Volume 2.22).

Table 13: Time to Progression (in days) from Randomization: ITT Population

	IL-2		Histamine +IL-2		Unadjusted P-value (Log-rank test)
		95% C.I.		95% C.I.	
Time to First Progression					
N	153		152		
# Progressed	139		128		
# Censored	14		24		
Median	86	84, 88	89	86, 92	0.0375
Time to Last Progression					
N	153		152		
# Progressed	134		121		
# Censored	19		31		
Median	100	87, 126	131	113, 144	0.0104

Table 14: Time to Progression (in days) from Randomization: ITT-LM Population

	IL-2		Histamine +IL-2		Unadjusted P-value (Log-rank test)
		95% C.I.		95% C.I.	
Time to First Progression					
N	74		55		
# Progressed	70		46		
# Censored	4		9		
Median	84	82, 86	85	84, 90	0.0074
Time to Last Progression					
N	74		55		
# Progressed	68		43		
# Censored	6		12		
Median	87	83, 103	128	89, 169	0.0033

Reviewer's Comments:

1. The P-values presented in Tables 15 and 16 were not adjusted for the use of multiple hypotheses testing procedures.
2. In the analysis of time to first progression in the ITT population, of the total of 139/153 who were analyzed as progressed, only 97/153 in the IL-2 arm were recorded as progressed, where as 42/153 (27.5%) were dead. In the IL-2 + histamine arm, of the total of 128/152 who were analyzed as progressed, only 99/152 were recorded as progressed, where as 29/152 (19.1%) were dead.
3. In the analysis of time to last progression in the ITT population, of the total of 134/153 who were analyzed as progressed, only 84/153 in the IL-2 arm were recorded as progressed, where as 50/153 (32.7%) were dead. In the IL-2 + histamine arm, of the total of 121/152 who were analyzed as progressed, only 85/152 were recorded as progressed, where as 36/152 (23.7%) were dead.
4. In the analysis of time to first progression in the ITT-LM population, of the total of 70/74 who were analyzed as progressed, only 46/74 in the IL-2 arm were recorded as progressed, where as 24/74 (32.4%) were dead. In the IL-2 + histamine arm, of the total of 46/55 who were analyzed as progressed, only 35/55 were recorded as progressed, where as 11/55 (20.0%) were dead.
5. In the analysis of time to last progression in the ITT-LM population, of the total of 68/74 who were analyzed as progressed, only 41/74 in the IL-2 arm were recorded as progressed, where as 27/74 (36.5%) were dead. In the IL-2 + histamine arm, of the total of 43/55 who were analyzed as progressed, only 29/55 were recorded as progressed, where as 14/55 (25.5%) were dead.
6. Approximately a third of the patients were recorded as dead before evaluation of progression. Thus, the time to progression may not be a reliable measure of the actual time to progression.
7. Time to first progression should be considered as time to progression. A patient's first evaluation of progression is the final evaluation of progression.
8. There was no significant difference between the two treatment arms (p-value=0.07, log-rank test), if the time to first progression only among those recorded as progressed in the ITT population were evaluated.

9. There was no significant difference between the two treatment arms (p-value=0.06, log-rank test), if the time to first progression only among those recorded as progressed in the ITT–LM population were evaluated.
10. Time to progression is a secondary efficacy parameter and will be evaluated as such.

3.4.2 Tumor Response

The numbers of patients in the ITT population achieving a complete or partial response was 5/104 in IL-2 arm, and 5/109 in IL-2 + histamine arm. There was no significant difference between the two treatment arms with respect to tumor response. The numbers of patients in the ITT-LM population achieving a complete or partial response was 0/46 in IL-2 arm, and 2/37 in IL-2 + histamine arm. There was no significant difference between the two treatment arms with respect to tumor response in this subgroup.

3.4.3 Quality of Life

The sponsor has reported (page 81-82, volume 2.22), that there was no significant difference between the two treatment groups in the change of QWB-SA scores for the ITT population. Within the ITT-LM population, there was a significant difference over time between the two treatment groups in the change of QWB-SB scores. There were significant differences between the treatment groups in both ITT and ITT-LM populations for quality-adjusted survival.

Reviewer's Comment:

This data is still under review and the results claimed by the sponsor have not been verified at this time.

4. Summary and Conclusions

This NDA submission is to support subcutaneous administration of histamine dihydrochloride with IL-2 as therapy for metastatic malignant melanoma patients with liver metastasis.
In this NDA submission, study MP-US-M01 is the only randomized pivotal study conducted for the efficacy and safety of histamine dihydrochloride. This open-label study was designed to evaluate the efficacy and safety of combined immunotherapy with histamine dihydrochloride + IL-2 versus IL-2 alone in patients with metastatic melanoma. This study enrolled a total of 305 patients with 153 patients who received IL-2 alone and 152 patients who received histamine dihydrochloride + IL-2. The primary efficacy endpoint of this study was survival. There was no statistically significant difference between the two treatment arms in the ITT population (log-rank test, P-value=0.1255). There was apparent difference in survival between the two treatment arms in the non-randomized subgroup ITT-LM population (log-rank test, P-value=0.004). Although two stratification factors, presence or absence of liver metastasis, and prior DTIC or no DTIC therapy, were specified in the protocol, the randomization was not stratified by these two factors.

1. Only one randomized open-label study conducted in patients with metastatic malignant melanoma, which failed to demonstrate efficacy as per the design of the study, in the intent-to-treat population (log-rank test, P-value = 0.1255).

   One should note that the protocol did not specify the time at which the final analysis would be conducted. The current time of analysis seems some what arbitrary, and the analysis is not adjusted for possible multiple looks.

2. When the overall result fails to show efficacy, usually subgroup findings are not acceptable and subgroup analyses at best can be exploratory or hypothesis generating analyses (ICH E-3 guidelines, section 11.4.2.8: *These analyses are not intended to "salvage" an otherwise non-supportive study but may suggest hypotheses worth examining in other studies or be helpful in refining labelling information, patient selection, dose selection etc.*). When one starts to do multiple subgroup testing, one can easily make a false positive claim based on such subgroup analysis. We do not know how to interpret the P-values based on such post-hoc analysis. Furthermore, without replication of the results in a second well-controlled study, the subgroup analysis can not be ruled out for a false positive result.

3. The sponsor wishes to claim approval based on a subgroup of non-randomized patients with liver metastasis. This subgroup hypothesis corresponding to liver metastasis was not stated as a hypothesis of interest to be tested in the original protocol. Any subgroup hypothesis needs to be stated in the protocol and accordingly proper allocation of α has to be specified. Otherwise, such post-hoc subgroup claim will inflate Type I error and it is difficult to interpret such P-values.

4. Liver metastasis was not a stratification factor prior to randomization. Thus there are significant imbalances due to non-stratification of the subgroup (significant imbalance in the number of patients with liver metastasis in ITT population, and significant imbalance in the number of patients with one metastatic disease site in the ITT-LM subgroup).

5. The imbalances are likely to be driving the difference in survival in the subgroup. Even though not significant, there were imbalances in the subgroup of patients with liver metastasis in the distribution of number of patients between the treatment arms with respect to age group, baseline LDH, performance status, sex, prior chemotherapy, number of metastatic sites, lymph node, lung and CNS metastases, disease-free survival since the initial diagnosis of primary tumor to initial metastasis, baseline albumin and time from initial metastasis to randomization, all favoring the IL-2+histamine arm, except LDH.

6. Sponsor's analyses adjusted for covariates are questionable. Results of the adjusted analyses are sensitive to inclusion or exclusion of a covariate. P-values for treatment effect range from 0.0017 to 0.1193 in the liver metastasis subgroup alone. Furthermore, when appropriately adjusted for multiplicity, treatment differences are unlikely to be significant in the subgroup of patients with liver metastasis. P-values can not be taken at face value and subgroup analyses are not believable.

7. Opposite trend is observed in the subgroup of patients with no liver metastasis.

8. The claims of improved efficacy in the liver metastasis subgroup could be a false positive result and requires future studies to evaluate this hypothesis. Literature suggests that this disease has a very heterogeneous prognosis and therefore, replication of the results, are essential (**See Appendix I**).

9. The compliance of the treatment by the patients is not studied in detail. This is an important issue since the current study is an open-label study and treatment is self-administered by the patients.

In this reviewer's opinion the study failed to demonstrate benefits of histamine dihydrochloride + IL-2 over IL-2 alone for patients with metastatic malignant melanoma. According to the usual requirement of the Agency for approval for marketing a new drug, the drug sponsor needs to demonstrate the efficacy of the new drug in at least two independent well-controlled clinical trials. In case that there is only one pivotal efficacy study, like this NDA submission, the evidence of the drug efficacy needs to be much stronger to be convincing. Furthermore, survival advantage in a single subgroup of patients with liver metastasis based on post-hoc analysis can not lead to approval, given that stratified randomization was not implemented and there is evidence of imbalance with respect to baseline demographic and prognostic factors in this subgroup of patients. It is not evident that the apparent survival advantage observed in the subgroup of liver metastasis patients is attributable solely to the treatment effect and not due to imbalances in known and unknown prognostic factors. Therefore, the evidence submitted in this application is not convincing and does not support approval.

Rajeshwari Sridhara, Ph.D.
Mathematical Statistician

Concur: Dr. Chen

Dr. Mahjoob

Cc:
Archival: NDA 21-240
HFD-150/ Mr. S. Bradley
HFD-150/ Dr. J. Chiao
HFD-150/ Dr. D. Griebel
HFD-150/ Dr. R. Pazdur
HFD-710/ Dr. G. Chi
HFD-710/ Dr. K. Mahjoob
HFD-710/ Dr. G. Chen
HFD-710/ Dr. R. Sridhara
HFD-710/ Chron

This review consists of 25 pages of text
SRIDHARA/MSWord - C:\NDA\Maxim\21240\m01\reviewf.doc

APPENDIX I

Literature Review

1. Cocconi, et. al. (N Engl J Med 327: 516-523, 1992) reported results of a randomized study conducted by the Italian Oncology Group for Clinical Research (GOIRC), in metastatic malignant melanoma. In this study 117 patients with metastatic malignant melanoma were randomly assigned to treatment with dacarbazine alone or dacarbazine in combination with tamoxifen. Patients were assigned to one of the two treatment regimens over the telephone by the GOIRC's operations office in Parma. Allocation was carried out in randomly permuted blocks of two, within strata defined according to the medical center, the extent of disease (loco-regional or disseminated), sex, age (≤ 50 years or > 50 years), and the dominant disease site (soft tissue with or without involvement of bone, or viscera). The overall survival was longer (median 48 vs 29 weeks, P-value=0.02) among the patients who received dacarbazine + tamoxifen than among those who received dacarbazine alone. Also in the subgroup of women, the survival (69 vs 30 weeks, P-value=0.008) were better with dacarbazine plus tamoxifen (D+T) than with dacarbazine alone (D).

2. Falkson et. al. (J.C.O. 16(5):1743-1751, 1998) reported results of randomized study conducted by the Eastern Cooperative Oncology Group Study (ECOG), in patients with metastatic malignant melanoma . In this study 271 patients were randomized in a 2x2 factorial design to receive one of the four treatment regimens: dacarbazine (69 patients), dacarbazine + INF-α-2b (68 patients), dacarbazine + tamoxifen (66 patients),or dacarbazine + INF-α-2b + tamoxifen (68 patients). Patients were stratified according to sex (men vs women) and the most clinically significant metastatic disease site (namely, hepatic vs other). The randomization used permuted blocks of size two within the stratum for each participating institution. The log-rank test for survival distributions across the four treatment arms suggested no significant differences in the overall survival across the treatment arms (P-value=0.85). The estimates of median survival ranged from 7.97 to 9.99 months. When a variable selection procedure using Cox proportional hazard model was conducted, the factors that were not significant were treatment, age, lymph node metastases, liver metastases, bone metastases, and subcutaneous metastasis. Furthermore, log-rank tests of treatment arms with and without tamoxifen for women were not significant for the end point of overall survival (p-value=0.97).

3. Bedikian, et. al. (Cancer 76(9):376-381, 1995) in their review of treatment of Uveal melanoma metastatic to the liver, report that the median survival from diagnosis of liver metastasis was 7 months with a range of 1-59 months, in this retrospective study of patients with Uveal melanoma metastatic to the liver.

4. Yusuf, et.al. (JAMA 266(1):93-98, 1991) have discussed in detail regarding the analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. They believe that the overall average result of randomized clinical trial is usually a more reliable estimate of treatment effect in various subgroups examined than are the observed effects in individual subgroups.

Reviewer's Comments:

GOIRC randomized study had significant difference in the overall survival between the treatment arms in the ITT population, as well as significant difference in survival in the subgroup of female patients, with D+T treatment having superior survival over D alone. However, these results could not be replicated in the ECOG randomized study and there were no significant differences in the overall survival among the 4 treatment arms. In fact the D alone arm had the largest estimated median survival of 9.99 months compared to 7.97 months in the D+T arm in this ECOG study. Furthermore, the difference in survival among the subgroup of female patients reported in the GOIRC study, could not be replicated in the ECOG study. Both these to studies and Bedikian et. al. report suggest that metastatic malignant melanoma is a heterogeneous disease and replication of studies are important to confirm efficacy results.